

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/009621

International filing date (day/month/year)
28.08.2004

Priority date (day/month/year)
18.09.2003

International Patent Classification (IPC) or both national classification and IPC
C07C67/343, C07C69/734, C07C51/353, C07C59/64

Applicant
DEGUSSA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/009621

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/009621

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-4
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-4
Industrial applicability (IA)	Yes: Claims	1-4
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

D1: JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, 1996, pages 4783 - 4803
D2: JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, 1998, pages 3041-3047
D3: US-A-4 081 475
D4: US-A-3 721 704

SECTION V:

Novelty - The subject-matter of claim 1 meets the requirements of Article 33(2) PCT since the cited prior art does not describe specifically the production of α -alkoxy / hydroxy - β -(p-hydroxyphenyl)- propionic acid derivatives of general formula (I) by the alkylation reaction of α -alkoxy / α -phenoxy or simply hydroxy- substituted acetic esters with p-hydroxybenzyl derivatives.

Inventive step - The set of claims on file meets an objection of lack of inventive step under Article 33(3) PCT as a surprising/ unexpected effect for the subject-matter claimed is not evident.

There are indeed clear indications in the prior art connecting the preparation of the compounds similar to the present compounds of general formula (I) by **the alkylation reaction of a reactive substituted benzyl derivative** (see D1: page 4784, Scheme 1 / Scheme 3: "benzyl halides"; see D2: page 3042: Scheme 1 and Table 1, $\text{PhCH}_2\text{-X}$, whereby X is halide, e.g., Br; see D3: column 2, lines 55-70, 4-hydroxybenzyl bromide / chloride; see D4: column 4, lines 30-40, substituted 4-hydroxybenzyl chloride) **with a compound of general formula $\text{R}_1\text{-O-CHX-COOR}_2$** (see D1: page 4784, Scheme 1 / Scheme 3; page 4787, Table 1; see also pages 4794 and 4795 "**General Method A**" and page 4796 "**General Method C**"; see D2: page 3042: **Scheme 1, first equation** and Table 1 for the definitions, in particular see the definitions for compound 19; see D3: **column 2, lines 20-35** and 40-54; column 2, lines 60-69; Examples; see D4: **column 4, lines 15-68; column 5, lines 15-29**; Examples 1-4). Differences between the present application and the documents described in the art relate to details in the structure of the reagents. These details, e.g. the presence / absence of an hydroxy group on the phenyl ring of the benzyl halide reagent, the substitution of the acetic ester, however, do not influence at all the chemistry involved in the alkylation of, for example, a malonate type compound at the C2 position with an alkyl halide in the presence of a base.

SECTION VIII:

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/009621

A problem of lack of clarity within the meaning of Article 6 PCT is present with regard to the present application, in particular with regard to the following expressions used in claim 1: "X is a group having an electron-attracting effect", "Y represents a nucleofugal leaving group" and "R¹, R² and X can assume the meaning stated above". These expressions are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear.

The final compound obtained in Example 3 appears incorrect in view of the presence of the reagent (C).